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Review Article

Magnesium in Human Health and Disease: A Review of Our Current Understanding

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Abstract

Magnesium (Mg) is an essential mineral in the human body which plays a fundamental role in energy production, oxidative phosphorylation, glycolysis and metabolic interactions with other nutrients including calcium, potassium and vitamin D. Mg deficiency can manifest as hypokalemia and hypocalcemia, leading to a host of neurological symptoms such as nystagmus and convulsions and cardiac symptoms including arrhythmia. Of considerable public health concern, low Mg intake and deficiency have been reported in various populations across the globe with different countries suggesting different recommended intakes of Mg. The current scientific literature indicates a number of potential adverse health consequences of low or deficient Mg status throughout the life course, including hypertension, cardiovascular disease, osteoporosis, and depression. However, given the heterogeneity in the populations recruited to interventional trials, doses and duration of Mg supplementation and disease states, there has been limited confirmatory evidence of the efficacy of Mg or the optimal intake for different populations. This review considers the current evidence-base on causes and consequences of Mg deficiency and the potential therapeutic utility of Mg in the treatment and prevention of human disease.

Keywords: *Magnesium; Blood Pressure; Cardiovascular Disease; Diabetes; Cancer; Osteoporosis; Migraines; Depression; Cognitive Function; Dementia*

Abbreviations

AD: Alzheimer's Disease; BP: Blood Pressure; BMD: Bone Mineral Density; T2DM: Diabetes Mellitus Type 2; Mg: Magnesium; Mg/d: milligram/day; NMDA: N-Methyl-D-Aspartate; NHANES: National Health and Nutrition Examination Survey; RCT: Randomized Controlled Trials; RR: Relative Risk; TRPM: Transit Receptor Potential Membrane Melastatin

Introduction

Magnesium (Mg) is an essential mineral in the human body, which acts as a cofactor in more than 300 enzymatic reactions. As the fourth most abundant cation in the body, Mg plays an important role in energy production, oxidative phosphorylation, glycolysis and nucleic acid synthesis [1]. Mg also interacts with other ions (such as potassium and calcium) which maintains nerve impulse conduction, cardiac electrical properties and muscle contraction [2]. Thus, Mg is indicated in the physiological function of the heart, brain and skeletal muscle.

The primary dietary sources of Mg include whole grains and grain products, nuts, fish and seafood, legumes and berries [3]. In addition, water can also contribute significantly to dietary intake. There is variability in the recommended Mg intake according to clinical guidelines around the world. In the United Kingdom, the recommended nutrient intake for Mg is 300 mg/d and 270 mg/d for men and women, respectively. Whilst the European Food Safety Authority defines adequate intake of Mg as 350 mg/d for men and 300 mg/d for females [3].

However, some concern has been expressed regarding insufficient Mg intakes amongst western populations and a recent report concluded that dietary intake of Mg in Western populations is below the recommended levels [4]. Similarly, data from the population-based National Health and Nutrition Examination Survey (NHANES) reported that the majority of the American population consumed insufficient Mg from food to maintain good health and that only with Mg supplementation could the population reach adequate intakes [5]. Whereas, in the UK population-based National Diet and Nutrition survey, 33% of adolescent boys and 47% of adolescent girls reported Mg intakes below the lower reference nutrient intake (LRNI). Furthermore, 75% of the Spanish population report Mg intake below the recommended intake [6].

Observational trials have reported significant associations between Mg and various health outcomes, including osteoporosis and bone fractures, diabetes, cancer, alcohol-related liver disease and hypertension and cardiovascular disease [7-10]. However, the overall benefits of Mg to health outcomes and disease states in humans remains unclear. Therefore, given the concerns of inadequate Mg intake across various populations and the potential impact upon population health, this review aims to provide an overview of the current evidence linking Mg to human health outcomes. Below, we provide an overview of the observational and interventional evidence linking Mg to different physical and psychological health outcomes and where possible, provide potential mechanistic insights.

Magnesium and health outcomes

Magnesium, blood pressure and cardiovascular disease

Mg has been shown to play fundamental roles in many physiological functions underpinning BP control in both *in vitro* and animal models. Mg can directly stimulate the production of prostacyclin and nitric oxide and thus influence endothelium-dependent and independent vasodilation subsequently impacting upon BP control. Furthermore, Mg has also been reported to influence vascular tone and reactivity and to prevent vascular injury by exerting antioxidant and anti-inflammatory functions. Whereas hypertension has shown to develop in rats which are magnesium deficient [11]. A large pool of observational trials have reported significant inverse associations between blood pressure/hypertension and Mg intake. For example, a large cross-sectional study of 16,684 adults from NHANES reported that individuals meeting the recommended Mg intake were at a significant 12% reduced risk of hypertension compared to those who were below the recommended intake level [12]. Such findings of an inverse association between dietary Mg and blood pressure/hypertension have also been reported in studies conducted within European populations [13]. Further support for an association between Mg and hypertension is reported in longitudinal studies. Specifically, in a follow-up study of 6,104 Chinese adults, those individuals in the highest quintile of Mg intake had a 20% reduction in risk of developing hypertension when compared to those in the lowest quintile [14].

Although a number of trials have reported significant associations between Mg intake and risk of hypertension and since 1925 Mg intervention has been recommended for BP lowering in patients with accelerated hypertension the results from intervention trials have been inconsistent and performed in relatively small cohorts. In one study, supplementation with Mg (368 mg/d) for 8 weeks in a sample of 14 healthy, normotensive young males did not significantly influence BP [15]. However, other human intervention trials have reported significant BP-lowering responses to Mg supplementation [16]. For instance, in a group of 70 participants with borderline hypertension, 4 weeks of magnesium-rich water had a significant reduction in BP [17]. The differences in trial outcomes can likely be explained by differences in trial design, specifically the duration of intervention, population (health status and age) and sample size. Nevertheless,

robust meta-analyses of RCTs report that Mg intervention significantly lowers BP in human participants. For example, Zhang., *et al*. (2012) found that in 34 RCTs with 2028 participants, oral Mg supplementation significantly reduced systolic BP by 2 (0.43 - 3.58) mmHg and diastolic BP by 1.78 (0.73 - 2.82) mmHg concluding that there is a causal effect of Mg supplementation on BP-lowering in adults. However, it is important to note the relatively small decreases in BP (although significant) and future well designed RCTs are required to determine optimal dosages and duration of intervention.

Hypertension has been associated with an increased risk of adverse health outcomes, including cognitive impairment and chronic kidney disease [18]. Hypertension is also the leading modifiable risk factor for heart and circulatory disease [19], and therefore, it is possible through modulating BP and endothelial function (as described above) Mg may lower the risk of cardiovascular events. Indeed, a cross-sectional study of the Framingham cohort in 2659 adults reported an inverse association between Mg intake and calcification of the coronary artery ($p < 0.001$), although no such association was reported for calcification of the abdominal artery [20]. Moreover, in the Nurses' Health Study with a median follow-up of 28 years, after controlling for coronary heart disease risk factors those in the highest quintile of Mg intake (> 342 mg/d) had a significantly lower risk of fatal coronary heart disease (RR = 0.61, 95% CI = 0.45 - 0.84) when compared to those in the lowest quintile (< 246 mg/d) [21].

In addition to coronary heart disease, significant associations have been reported for Mg intake and stroke risk. Specifically, in a meta-analysis of 8 cohort studies in 304,551 participants there was a significant inverse association between magnesium intake and total stroke incidents (RR = 0.89, 95% CI = 0.82 - 0.97, $I^2 = 0\%$) [9]. In line with these findings, [22] meta-analysis of 7 cohort studies incorporating 241, 378 participants reported a significant 8% reduction in stroke risk for every 100 mg/d increase in Mg intake. Whereas, in the European Prospective Investigation into Cancer and Nutrition study of 36, 094, 631 participants a significant 22% reduction in stroke risk for every 100 mg/d increment in Mg intake (hazard ratio = 0.78, 95% CI = 0.65 - 0.93) was reported [23].

Finally, the influence of low Mg levels on BP control may also have important implications in pregnancy and can pose a significant health risk for both the mother and newborn. Specifically, serum Mg levels are reported to be lower in women with pre-eclampsia compared to healthy control, with increased BP levels being significantly associated with higher urinary Mg excretion [24]. However, the effects of oral Mg supplementation on pregnancy and on the prevention of pre-eclampsia, have not been proved so far, leading to a need of high quality RCT in this population [24].

In summary, there is strong *in vitro*, animal model and human observational evidence suggesting the role of Mg in BP control, however interventional trials have not provided robust evidence for its beneficial use as a supplement. As a result, supplementation with Mg is not currently recommended for the prevention or treatment of hypertension (outside pre-eclampsia) by the several clinical guidelines for hypertension management including the ones from Canada. However, foods and nutrients high in magnesium are recommended as part of a healthy diet by the International Society of Hypertension Global Hypertension Practice Guidelines and the European Society of hypertension guidelines. Mg is recognized as a nonpharmacological intervention that has been reported to lower BP but the extent and/or quality of the supporting clinical trial evidence is less persuasive according to American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [25]. Future investigations are needed to elucidate the role of Mg supplementation in hypertension control and whether the influence of Mg on BP could translate in cardiovascular risk prevention.

Magnesium and diabetes mellitus type 2

A body of evidence has reported significant associations between low and deficient Mg status and insulin resistance and diabetes mellitus type 2 (T2DM). However, the direction of the relationship between Mg and T2DM has been subject to debate. Specifically, it has been suggested that hypomagnesemia is a biproduct of T2DM, as opposed to playing a direct role in the pathophysiology of the disease. This was based on a cohort study reporting that hypomagnesemia was prevalent in patients with T2DM, an observation not found in patients with prediabetes [26]. Indeed, T2DM has been linked to a number of Mg extracellular and intracellular abnormalities, with

lower cellular and ionized plasma Mg concentrations but with concurrent normal serum Mg concentrations in those with the disease [27]. Furthermore, T2DM has also been implicated in the depletion of Mg body stores by means of increased urinary excretion. However, evidence from human observational and interventional studies contradicts this hypothesis, suggesting the relationship between Mg and T2DM may be bidirectional.

The ion channel transit receptor potential membrane melastatin 6 and 7 (TRPM6 and TRPM7) play central roles in Mg homeostasis. Interestingly, it has been reported that individuals with common genetic polymorphisms of TRPM6 and TRPM7, leading to reduced activity are at an increased risk of hypomagnesemia with a concurrent possible increased risk of T2DM under conditions of low Mg intake [28]. Whereas a number of meta-analyses of cohort studies have reported significant associations between Mg intake and risk of T2DM. For example, an early meta-analysis [8] in 286,668 participants with 10,912 incidences of T2DM found a significant dose-dependent effect, whereby a 100 mg/d increase in Mg intake was associated with a 15% reduction in risk of developing T2DM. Such findings are supported by a later meta-analysis of 11 cohort studies which reported significant inverse associations between serum Mg concentrations and risk of T2DM [29]. Further cohort trials have reported significant associations between low Mg intake and increased T2DM risk across both Western and non-Western populations [30]. The most robust evidence for the protective effect of Mg on T2DM comes from a recent cost-effective analysis based upon results from a RCT assessing the efficacy of oral Mg in decreasing fasting glucose levels in individuals with prediabetes. Specifically, Guerrero-Romero., *et al*. (2022) [31] reported that in pre-diabetic men, oral Mg supplementation for 4 months led to a significant 22% reduction in the development of T2DM when compared to placebo. This led the authors to conclude that oral Mg supplementation is a cost-effective preventative measure for T2DM.

In addition to the prevention of T2DM there is also evidence that Mg supplementation may help to manage the disease. Mg deficiency in T2DM is reported to exacerbate complications, whilst Mg supplementation has been shown to protect against T2DM complications in those with the disease [32]. The early findings from Mg supplementation studies in participants with T2DM showed conflicting results in regard to improving insulin resistance and glycemic control [3]. A recent meta-analysis from 24 RCTs across 11 countries reported that oral Mg supplementation can significantly improve metabolic outcomes in T2DM [33]. Specifically, based on the meta-analysis, the authors concluded that oral Mg supplementation at a dose of 279 mg/d for 4 months, 429 mg/d for 3 months and 300 mg/d for 4 months are the optimal dosages and durations for the treatment of glycemic control, hyperlipidemia and hypertension in patients with T2DM.

In summary, the available mechanistic, human cohort and interventional trials indicate the relationship between Mg intake and T2DM is bidirectional, whereby the disease disrupts Mg homeostasis leading to reductions in Mg concentrations, but also low Mg intake predisposes individuals to an increased risk of the disease. Whereas oral Mg supplementation may improve the management of complications, including glycemic control, hyperlipidemia and hypertension in T2DM patients.

Magnesium and cancer

The relationship between Mg and cancer is one of great complexity, however, emerging evidence from animal and human observational trials suggests Mg may have anticarcinogenic effects. In a rat model Mg was shown to protect against 3-methylcholantrene induced fibrosarcoma and reduce ornithine decarboxylase activity in the intestinal mucous membrane, suggesting potential utility as a chemotherapeutic agent [34]. However, it is important to note that one early trial in an experimental tumor rat model reported that a Mg deficient diet reduced tumor growth through decreasing glutathione synthesis, which requires Mg as a cofactor [35]. Whereas Mg has been shown to inhibit nickel-induced carcinogenesis in the kidneys of rats and further nickel and lead-related lung cancers in mice [36].

A number of observational trials have identified an increased risk of certain cancers in those carrying polymorphisms in the aforementioned TRPM7 gene. For example, Shen., *et al*. (2014) [37] reported that the rs7173321 (G/C) polymorphism of TRPM7 was

significantly associated with an increased risk of breast cancer when compared to the CC genotype. Similarly, it has been reported in breast cancer patients there is a complex alteration in Mg homeostasis, whereby reduced plasma and erythrocytes Mg levels are accompanied with increases in urinary excretion of Mg, suggestive of Mg depletion in this disease [38]. Whereas a number of human cohort studies and meta-analyses of such studies have been conducted to elucidate the relationship between Mg intake and the risk of various different cancers. For example, a meta-analysis by Chen., *et al*. (2012) reported significant associations between Mg intake and colorectal cancer risk, a dose-response analysis indicated that for every 50 mg/d increment in Mg intake there was a 5% reduction in colorectal cancer risk. With a recent meta-analysis reporting that for every 100 mg/d increase in dietary Mg intake there is a significant 6% and 5% lower risk of all-cause and cancer mortality, respectively [39].

There is strong evidence indicating a protective effect of Mg on cancer risk, however, to our knowledge no RCT has investigated Mg supplementation as an anticarcinogenic agent in humans. Therefore, there is an urgent need for robust RCTs, investigating the impact of Mg intervention on cancer risk. Such evidence may help to provide future avenues for anticarcinogenic agents and provide policy makers with robust data to support the development of Mg reference intakes to support population health.

Magnesium and bone health

Approximately 50 - 60% of the total human body's Mg content is stored in the bones. Since Mg facilitates osteoblast proliferation, Mg deficiency has been implicated in decreases in bone formation. Moreover, Mg plays an important role in the activation of vitamin D to the metabolic active form of 1,25-dihydroxycholecalciferol and further in the transport of vitamin D. Therefore, through direct (inducing osteoblast proliferation) and indirect (activation and transport of vitamin D) Mg may play an important role in maintaining optimal bone mineral density (BMD) and bone mass and decreasing fracture and osteoporosis risk. Indeed, in Mg deficient rats, a significant reduction in osteoblast numbers and decreased bone mass has previously been reported with Mg deficient mice were shown to develop osteoporosis, increased skeletal fragility associated with impaired bone growth, increased bone resorption and decreased bone formation [40].

The majority of observational studies investigating the relationship between Mg intake and BMD, fracture and osteoporosis risk have been conducted in postmenopausal women. For example, a significant association was reported between serum Mg levels and BMD in postmenopausal women [7]. Whereas, in 73,684 postmenopausal women in the Women's Health Initiative Observational Study, BMD of the hip was 3% higher ($p < 0.001$) and whole-body BMD was 2% higher ($p < 0.001$) in those with Mg intakes at levels > 423 mg/d when compared to those who consumed < 207 mg/day [41]. The potential beneficial effect of Mg on bone health appears to also extend to men. Specifically, Kunutsor., *et al*. (2017) [42] reported strong significant associations between low serum Mg concentrations and risk of fractures.

There is limited available evidence from human intervention trials, which is predominantly restricted to postmenopausal women, although this evidence suggests beneficial effects of Mg supplementation on bone health. A seminal study of oral Mg supplementation (600 mg/d) for 12 months reported a significant increase in BMD by 11% amongst the women on the active intervention. However, the intervention also included adjuvant administration of a number of other nutrients including calcium and thus it was not possible to distinguish the isolated effect of Mg in this cohort [43]. However, in one study in postmenopausal osteoporotic women, which intervened with oral Mg in isolation reported significant increases in BMD following the 12-month intervention [44].

In summary, there is strong evidence from mechanistic, animal and human observational trials that Mg plays an important role in the maintenance of bone health and reducing the risk of bone fractures. However, there is a paucity of evidence from human intervention trials investigating the influence of Mg in isolation, of which, this is restricted to postmenopausal women. Such intervention trials investigating the influence of Mg supplementation on bone health and osteoporosis risk in large age and sex diverse cohorts are needed to confirm the beneficial effects of Mg supplementation on osteoporosis prevention and treatment.

Magnesium and brain health

Mg plays a major role in the maintenance of the central nervous system. Neuronal Mg is fundamental to the activation of N-methyl-D-aspartate (NMDA) receptor excitability. In turn, NMDA receptors are essential for excitatory synaptic transmission, excitotoxicity neuronal plasticity, and as such are fundamental to the processes of developmental plasticity, learning, and memory and thus cognition. Low levels of Mg in the central nervous system can lead to hyperexcitability of the NMDA receptor, causing an influx of calcium, which in turn leads to formation of reactive oxygen species and subsequent neuronal death. Through NMDA-dependent mechanisms Mg can also directly activate nitric oxide synthase, leading to increases in nitric oxide, a potent vasodilator, the bioavailability of which has been directly associated with cognition. Given the plethora of important roles Mg plays throughout the central nervous system, there has been great research into the ions potential to prevent and treat a number of different psychiatric conditions. Below, we outline the major areas of evidence to date.

Migraines

Migraine attacks have been associated with low concentrations of Mg in cerebrospinal fluid and peripheral serum [45]. Indeed, a number of RCT interventions have reported significant benefits of oral Mg supplementation on migraine frequency and intensity. For example, a multi-center, placebo-controlled, double-blind randomized trial reported that following 12 weeks of Mg intervention at a dose of 600 mg/d, a significant reduction in migraine attacks by 41.6% was observed. Moreover, the authors also reported that those in the Mg intervention group had significant reductions in the number of days with migraine and the quantity of drugs consumed for treatment [46]. Such findings are supported by a multicenter, crossover placebo-controlled trial, whereby 2 months intervention with oral Mg led to a significant reduction in the frequency of migraine attacks compared to placebo [47]. However, it is important to note that although the aforementioned studies reported that oral Mg is an effective therapeutic agent for migraine attacks compared to placebo, both trials also reported significant increases in gastrointestinal symptoms, a known side effect of large Mg dosages. Lower oral Mg supplementation (360 mg/d) for 2 months has also been reported to significantly reduced frequency and total pain index in women with menstrual migraine [48].

Taken the above evidence, the United States Headache Consortium recommends Mg for the prevention of migraine headaches. Oral Mg at high dosages can be an effective therapeutic agent for the treatment of migraine headaches in adults, however, this results in significant gastrointestinal side effects which must be considered before initiating treatment. Whereas lower dosage of Mg closer to the RDA have also reported therapeutic effects in patients with Migraine. Therefore, when implementing Mg as a therapeutic agent for migraines, it may be important to consider incremental Mg dosages, to optimize the therapeutic benefits of Mg but also limit the negative side effects of larger dosages.

Depression

As described previously, there are a number of pathways by which Mg can influence the central nervous system to potentially exert antidepressant effects, including direct interaction with the NMDA receptor, the dysfunction of which is a major causative factor in the pathology of depression. Indeed, a number of observational trials have reported a significant inverse association between Mg intake and depressive symptoms [49]. Moreover, patients with depression have also been shown to present with significantly lower cerebrospinal fluid, serum and erythrocyte Mg levels compared to healthy controls [50].

The first antidepressant effects of Mg in patients with depression was reported in 1921. However, there is a paucity of robust placebo-controlled human intervention trials intervening with Mg in isolation, reporting inconclusive results. For example, a 12-month RCT comparing the efficacy of Mg to the antidepressant medication imipramine in depressed elderly adults reported no significant difference in depressive symptoms between the 2 intervention groups [51]. Suggesting that Mg is as effective as the antidepressant medication imipramine in the treatment of depression, however, no placebo group was implemented in the study. Whereas one trial reported that

intravenous administration of Mg resulted in no significant change in depressive symptoms 8 days post infusion [52]. However, the trial was limited to 6 patients in the active Mg group and of a limited timeframe of 8 days, which may explain the null findings. Whereas a placebo-controlled randomized trial in 60 patients diagnosed with depression reported significant improvements in depression scores (as measured by the Beck Depression Inventory-II) when compared to the placebo. Indeed, the improvements in depression scores in the active intervention group were accompanied by significant increases in serum Mg concentrations. In addition, a recent meta-analysis of the available RCT evidence assessing the impact of Mg supplementation on depressive scores in adults with depressive disorders reported a significant reduction in depressive scores following supplementation with Mg compared to placebo [53]. However, this review included only 7 RCTs with 325 participants, highlighting the paucity of the evidence base relating to Mg supplementation and depression. This highlights the need for further robust, large scale RCTs investigating the efficacy of oral Mg supplementation as an antidepressant agent. Such evidence is required to delineate the role of Mg in the prevention and treatment of depression, with the potential to have significant public health implications.

Cognitive decline and neurodegenerative diseases

As described previously, Mg plays a plethora of different roles across the central nervous system, such as direct activation upon NMDA receptors and calcium antagonistic actions. Moreover, it has been reported that Mg may inhibit amyloid protein precursor processing and abnormal tau protein phosphorylation, alongside inducing toxin clearance and reducing neuroinflammation. Such neuroprotective processes would likely induce cognitive benefits and potentially reduce the risk of neurodegenerative diseases such as dementia. Indeed, in support of this suggestion, Mg intervention has been shown to decrease beta-amyloid deposits and reduce neuroinflammation in an animal model of Alzheimer's Disease (AD) whilst also improving working and short-term and long-term memory and increase learning abilities in another animal model [54].

A number of different avenues of evidence have linked Mg intake to cognition and neurodegenerative diseases such as dementia in humans. For instance, postmortem examination of AD patients' brains has shown significantly decreased Mg concentrations when compared to healthy controls, whilst Mg depletion has been observed in the hippocampus of AD patients, a brain region significantly involved in the pathophysiology of the disease [55]. Whereas a systematic review of 13 cross-sectional studies compared Mg levels between dementia patients and healthy controls [56]. The authors reported that AD patients had significantly lower Mg concentrations in hair samples and cerebrospinal fluid compared to healthy controls but no differences were reported for serum or plasma. Such findings provide support for the potential role of Mg in protecting cognitive function and reducing dementia risk. However, this also highlights the need for future research aimed at elucidating the mechanisms by which Mg may influence dementia risk and further the requirement for standardized measurements of Mg in different bodily compartments, to allow direct comparison across different studies.

Longitudinal trials have also investigated the association between Mg intake and risk of mild cognitive impairment and dementia, which provides further evidence for the role of Mg in neurodegenerative disease. For example, in a cohort of 1,400 healthy men with a follow-up of 8 years, greater Mg intake was associated with a significant decreased risk of developing mild cognitive impairment [57], a major risk factor for dementia. Furthermore, another study in community-dwelling adults aged > 60 years with a 17-year follow-up reported that participants with a Mg intake > 200 mg/d had a significant 37% reduction in risk of developing dementia and a 74% reduced risk of vascular dementia specifically. Although animal trials and epidemiological evidence strongly indicates a protective role of higher Mg intake on cognitive function and risk of dementia, only a small number of robust RCT have been conducted to investigate the efficacy of Mg in preventing cognitive decline and reducing dementia risk.

To our knowledge, only 2 RCTs in humans have investigated the impact of oral Mg supplementation on cognitive outcomes. Specifically, building upon the aforementioned animal models of AD, Liu., *et al.* (2015) [58] investigated the efficacy of 12-week intervention with Mg on cognitive function in male and female adults aged between 50 and 70 with self-reported memory complaints. The authors reported

significant improvements in various domains of cognitive function, including executive functioning and working and episodic memory, alongside significant improvements in cognitive ability (determined by a composite score). More recently, the second RCT also intervened with Mg in 109 adults aged 18-65 years for 30 days and assessed cognitive outcomes. The study reported significant improvements in all cognitive domains assessed following the 30-day intervention, encompassing learning, recall, memory and overall cognitive abilities [59]. However, it is important to note that the trial supplement also included a number of additional nutrients known to influence cognitive function, including Vitamin B6 [60]. Therefore, it is not possible to delineate the isolated effects of Mg in this trial.

In summary, there is a wealth of mechanistic and animal evidence indicating that Mg plays an important role in cognitive function. A large number of human observational trials suggest Mg may play a role in protecting cognitive function and subsequently reducing dementia risk. However, there is a paucity of robust placebo-controlled human intervention trials investigating the influence of Mg supplementation on cognitive function. Such well-controlled large-scale trials are urgently needed.

Conclusion and Research Priorities

Mg is an essential mineral which plays a fundamental role throughout the human body, including energy production, oxidative phosphorylation, glycolysis and nucleic acid synthesis and also has important metabolic interactions with other nutrients, including potassium, calcium and vitamin D. Given its numerous functional roles, Mg is essential in the maintenance of human health and disease prevention across the life cycle. Mg is widely recognized as an essential mineral as part of a healthy and balanced diet which should be encouraged by medical professionals. Correspondingly, Mg deficiency contributes to a number of significant adverse health outcomes and diseases. Of significant public health concern is the low Mg intake reported across various populations, with suggestions that Mg supplementation may be an effective means to correct inadequate dietary intakes.

Animal trials and epidemiological studies suggest that Mg could play a role in the prevention and/or treatment of certain forms of cancer, osteoporosis and cardiovascular disease. Human RCTs based on Mg supplementation suggest a beneficial effect in various health conditions including hypertension, T2DM and migraine headaches with preliminary data showing promising results in depression and cognitive impairment. However, large scale interventional trials are lacking and are urgently needed to fill gaps in knowledge and influence health policy at national and international levels.

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Bibliography

1. Saris NEL., *et al*. "Magnesium: An update on physiological, clinical and analytical aspects". *Clinica Chimica Acta* 294.1-2 (2000): 1-26.
2. Volpe SL. "Magnesium in disease prevention and overall health". *Advances in Nutrition* 4.3 (2013): 378S-383S.
3. Panel E and Nda A. "Scientific opinion on dietary reference values for magnesium". *EFSA Journal* 13.7 (2015): 1-63.
4. Cazzola R., *et al*. "Going to the roots of reduced magnesium dietary intake: A tradeoff between climate changes and sources". *Heliyon* 6.11 (2020): e05390.
5. Veronese N., *et al*. "Magnesium and health outcomes: an umbrella review of systematic reviews and meta-analyses of observational and intervention studies". *European Journal of Nutrition* 59.1 (2020): 263-272.

6. Olza J., *et al*. "Reported dietary intake, disparity between the reported consumption and the level needed for adequacy and food sources of calcium, phosphorus, magnesium and vitamin D in the Spanish population: findings from the ANIBES study". *Nutrients* 9.2 (2017): 168.

7. Mederle OA., *et al*. "Correlations between bone turnover markers, serum magnesium and bone mass density in postmenopausal osteoporosis". *Clinical Interventions in Aging* 13 (2018): 1383-1389.

8. Larsson SC and Wolk A. "Magnesium intake and risk of type 2 diabetes: a meta-analysis". *Journal of Internal Medicine* 262.2 (2007): 208-214.

9. Nie ZL., *et al*. "Magnesium intake and incidence of stroke: meta-analysis of cohort studies". *Nutrition, Metabolism and Cardiovascular Diseases* 23.3 (2013): 169-176.

10. Hernández-Rubio A., *et al*. "Associations of hypomagnesemia in patients seeking a first treatment of alcohol use disorder". *Drug and Alcohol Dependence* 245 (2023): 109822.

11. Ryan MP and Brady HR. "The role of magnesium in the prevention and control of hypertension". *Annals of Clinical Research* 16.43 (1984): 81-88.

12. Wabo TMC., *et al*. "Association of dietary calcium, magnesium, sodium, and potassium intake and hypertension: a study on an 8-year dietary intake data from the National Health and Nutrition Examination Survey". *Nutrition Research and Practice* 16.1 (2022): 74-93.

13. Van Leer EM., *et al*. "Dietary calcium, potassium, magnesium and blood pressure in the Netherlands". *International Journal of Epidemiology* 24.6 (1995): 1117-1123.

14. Jiao Y., *et al*. "Relationship between dietary magnesium intake and metabolic syndrome". *Nutrients* 14.10 (2022): 2013.

15. Cosaro E., *et al*. "Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome". *Nutrition, Metabolism and Cardiovascular Diseases* 24.11 (2014): 1213-1220.

16. Guerrero-Romero F and Rodríguez-Morán M. "The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial". *Journal of Human Hypertension* 23.4 (2009): 245-251.

17. Rylander R and Arnaud MJ. "Mineral water intake reduces blood pressure among subjects with low urinary magnesium and calcium levels". *BMC Public Health* 4 (2004): 56.

18. Jarrett Harry., *et al*. "Blood pressure and hypertension in relation to cognitive performance in older Irish adults from the TUDA cohort: Preliminary analysis". *Journal of Human Hypertension* 32 (2018): 707-708.

19. Zhou B., *et al*. "Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants". *Lancet* 398.10304 (2021): 957-980.

20. Hruby A., *et al*. "Magnesium intake is inversely associated with coronary artery calcification: the Framingham Heart Study". *JACC Cardiovasc Imaging* 7.1 (2014): 59-69.

21. Chiuve SE., *et al*. "Dietary and plasma magnesium and risk of coronary heart disease among women". *Journal of the American Heart Association* 2.2 (2013): e000114.

22. Larsson SC., *et al*. "Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies". *American Journal of Clinical Nutrition* 95.2 (2012): 362-366.

23. Sluijs I., *et al*. "Intakes of potassium, magnesium, and calcium and risk of stroke". *Stroke* 45.4 (2014): 1148-1150.

24. Rylander R. "Magnesium in pregnancy blood pressure and pre-eclampsia - A review". *Pregnancy Hypertension* 4.2 (2014): 146-149.

25. Whelton PK., *et al*. "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines". *Hypertension* 71.6 (2018): E13-115.

26. Simmons D., *et al*. "Hypomagnesaemia is associated with diabetes: Not pre-diabetes, obesity or the metabolic syndrome". *Diabetes Research and Clinical Practice* 87.2 (2010): 261-266.

27. Barbagallo M., *et al*. "Serum ionized magnesium in diabetic older persons". *Metabolism* 63.4 (2014): 502-509.

28. Song Y., *et al*. "Common genetic variants of the ion channel transient receptor potential membrane melastatin 6 and 7 (TRPM6 and TRPM7), magnesium intake, and risk of type 2 diabetes in women". *BMC Medical Genetics* 10 (2009): 4.

29. Wu J., *et al*. "Circulating magnesium levels and incidence of coronary heart diseases, hypertension, and type 2 diabetes mellitus: a meta-analysis of prospective cohort studies". *Nutrition Journal* 16.1 (2017): 60.

30. Kim DJ., *et al*. "Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes". *Diabetes Care* 33.12 (2010): 2604-2610.

31. Guerrero-Romero F and Nevárez-Sida A. "Cost-effectiveness analysis of using oral magnesium supplementation in the treatment of prediabetes". *Primary Care Diabetes* 16.3 (2022): 435-439.

32. Feng J., *et al*. "Role of magnesium in type 2 diabetes mellitus". *Biological Trace Element Research* 196.1 (2020): 74-85.

33. Xu L., *et al*. "Effects of magnesium supplementation on improving hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes: A pooled analysis of 24 randomized controlled trials". *Frontiers in Nutrition* 9 (2023): 1020327.

34. Mori H., *et al*. "Chemoprevention by naturally occurring and synthetic agents in oral, liver, and large bowel carcinogenesis". *Journal of Cellular Biochemistry. Supplement* 27 (1997): 35-41.

35. Mills BJ., *et al*. "Magnesium deficiency inhibits biosynthesis of blood glutathione and tumor growth in the rat (42260)". *Proceedings of the Society for Experimental Biology and Medicine* 181.3 (1986): 326-332.

36. Kasprzak KS., *et al*. "Iron accelerates while magnesium inhibits nickel-induced carcinogenesis in the rat kidney". *Toxicology* 90.1-2 (1994): 129-140.

37. Shen B., *et al*. "The association between single-nucleotide polymorphisms of TRPM7 gene and breast cancer in Han Population of Northeast China". *Medical Oncology* 31.7 (2014): 51.

38. Bezerra DLC., *et al*. "Hypomagnesemia and its relationship with oxidative stress markers in women with breast cancer". *Biological Trace Element Research* 199 (2021): 4466-4474.

39. Bagheri A., *et al*. "Total, dietary, and supplemental magnesium intakes and risk of all-cause, cardiovascular, and cancer mortality: A systematic review and dose-response meta-analysis of prospective cohort studies". *Advances in Nutrition* 12.4 (2021): 1196-1210.

40. Rude RK., *et al*. "Skeletal and hormonal effects of magnesium deficiency". *Journal of the American College of Nutrition* 28.2 (2009): 131-141.

41. Orchard TS., *et al*. "Magnesium intake, bone mineral density, and fractures: results from the Women's Health Initiative Observational Study". *American Journal of Clinical Nutrition* 99.4 (2014): 926-933.

42. Kunutsor SK., *et al*. "Low serum magnesium levels are associated with increased risk of fractures: a long-term prospective cohort study". *European Journal of Epidemiology* 32.7 (2017): 593-603.

43. Abraham GE. "The importance of magnesium in the management of primary postmenopausal osteoporosis". *Journal of Nutritional Medicine* 2.2 (1991): 165-178.

44. Abdelazim IA., *et al*. "Effect of raloxifene hydrochloride on bone mineral density and bone turnover in Kuwaiti postmenopausal women with osteoporosis". *Archives of Osteoporosis* 9 (2014): 189.

45. Ramadan NM., *et al*. "Low brain magnesium in migraine". *Headache* 29.9 (1989): 590-593.

46. Peikert A., *et al*. "Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study". *Cephalalgia* 16.4 (1996): 257-263.

47. Taubert K. "Magnesium in migraine. Results of a multicenter pilot study". *Fortschritte der Medizin* 112.24 (1994): 328-330.

48. Facchinetti F., *et al*. "Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium". *Headache* 31.5 (1991): 298-301.

49. Li B., *et al*. "Dietary magnesium and calcium intake and risk of depression in the general population: A meta-analysis". *Australian and New Zealand Journal of Psychiatry* 51.3 (2017): 219-229.

50. Rechenberg K. "Nutritional interventions in clinical depression". *Clinical Psychological Science* 4.1 (2016): 144-162.

51. Barragan-Rodríguez L., *et al*. "Depressive symptoms and hypomagnesemia in older diabetic subjects". *Archives of Medical Research* 38.7 (2007): 752-756.

52. Mehdi SMA., *et al*. "Double-blind, randomized crossover study of intravenous infusion of magnesium sulfate versus 5% dextrose on depressive symptoms in adults with treatment-resistant depression". *Psychiatry and Clinical Neurosciences* 71.3 (2017): 204-211.

53. Moabedi M., *et al*. "Magnesium supplementation beneficially affects depression in adults with depressive disorder: a systematic review and meta-analysis of randomized clinical trials". *Frontiers in Psychiatry* 14 (2023): 1333261.

54. Slutsky I., *et al*. "Enhancement of learning and memory by elevating brain magnesium". *Neuron* 65.2 (2010): 165-177.

55. Andrási E., *et al*. "Disturbances of magnesium concentrations in various brain areas in Alzheimer's disease". *Magnesium Research* 13.3 (2000): 189-196.

56. Veronese N., *et al*. "Magnesium status in Alzheimer's disease: A systematic review". *American Journal of Alzheimer's Disease and Other Dementias* 31.3 (2016): 208-213.

57. Cherbuin N., *et al*. "Dietary mineral intake and risk of mild cognitive impairment: The PATH through Life Project". *Frontiers in Aging Neuroscience* 6 (2014): 4.

58. Liu G., *et al*. "Efficacy and safety of MMFS-01, a synapse density enhancer, for treating cognitive impairment in older adults: A randomized, double-blind, placebo-controlled trial". *Journal of Alzheimer's Disease* 49.4 (2015): 971-990.

59. Zhang C., *et al*. "A Magtein®, magnesium L-threonate, -based formula improves brain cognitive functions in healthy Chinese adults". *Nutrients* 14.24 (2022): 5235.

60. Jarrett H., *et al*. "Vitamin B-6 and riboflavin, their metabolic interaction, and relationship with MTHFR genotype in adults aged 18-102 years". *American Journal of Clinical Nutrition* 116.6 (2022): 1767-1778.

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